## REMARKS

### Introductory Comments

Claims 1, 3, 5-7, 11-14 and 19-21 were examined in the Office Action under reply and stand rejected under (1) 35 U.S.C. §112, first paragraph (claims 1, 3, 5-7, 11-14 and 19-21); and (2) 35 U.S.C. §112, second paragraph (claims 19 and 20). These rejections are traversed and believed to be overcome for reasons discussed below.

### Overview of the Above Amendments

Claims 19-21 have been amended to recite the invention with greater particularity. Specifically, the concluding statement in claims 19 and 20 has been amended to recite that the method treats or prevents "cerebellar neuronal degeneration." Additionally, claims 19 and 21 have been amended to recite that administration is to "a cerebellar lobe" of the subject. Support for these amendments can be found in the claims as filed, as well as throughout the specification at e.g., page 25, line 13.

### Rejections Under 35 U.S.C. §112, First Paragraph

The Office rejected all pending claims under 35 U.S.C. §112, first paragraph as nonenabled. With respect to claims 1-3, 5, 11 and 12, the Office correctly notes these claims encompass both *in vitro* and *in vivo* applications but argues the "only *in vivo* use asserted is for gene therapy" and "the specification fails to adequately teach how to use the claimed methods therapeutically." Office Action, page 3. The Examiner further states: "The specification must teach how to use the claimed invention *in vivo*." Office Action, page 5. Regarding claims 6, 7, 13, 14 and 19-21, the Office argues these claims are exclusively directed to *in vivo* methods and do not encompass *in vitro* applications and are therefore not enabled. Office Action, page 7.

The Office supports this assertion citing Rubanyi et al., *Molec. Aspects Med.* (2001) 22:113-142 ("Rubanyi") as representing the state of the art at the time the application was filed. In particular, the Examiner asserts Rubanyi discusses the technical

hurdles that remain to be overcome in developing effective gene therapy techniques. These include problems with gene delivery vectors and improvement of gene expression control systems. Office Action, pages 4-5, bridging paragraph. However, applicants have overcome each of the hurdles described in Rubanyi. In particular, applicants have shown that *in vivo* administration using a lentiviral vector as the gene delivery system provides for efficient expression of the gene contained within the vector in Purkinje cells. As explained in the specification at page 33, lines 8-12:

> A two microliter injection ($10^4 - 10^5$ infectious units) into a single lobule transduced up to 1500 Purkinje cells. With an estimated 20,000 Purkinje cells in all 10 lobules of the mouse cerebellum approximately 10% of all Purkinje cells and close to 100% of the injected lobule were transduced.

The transduction of the Purkinje cells, which are cerebellar neurons, was detected based on expression and biological activity of the β-galactosidase protein.

Nevertheless, the Examiner ignores this finding and states that applicants have taught only β-galactosidase expression and that one of skill in the art would not expect β-galactosidase expression to have a therapeutic effect. Contrary to the Examiner's assertions, applicants are not asserting that β-galactosidase provides a therapeutic effect. Rather, β-galactosidase is used as a measure of transduction efficiency and is indeed indicative of therapeutic efficacy. In fact, β-galactosidase is routinely used and relied on by scientists in the discipline of gene therapy as predictive of whether a particular gene delivery system can provide a therapeutic benefit when used to deliver a therapeutic gene of interest.

To evidence that the β-galactosidase gene (lacZ) is routinely used to study transgene delivery and expression and is indeed predictive of a therapeutic benefit, applicants are providing a number of papers and abstracts related to delivery of the lacZ gene to the CNS. All of these papers and abstracts are from well-respected, peer-reviewed journals and are therefore probative evidence of the credibility of the lacZ system for predicting therapeutic utility. For example, Alisky et al., *NeuroReport* (2000)

11:2669-2673 relates to the delivery of the lacZ gene with FIV vectors, using the identical system described in the present patent application. The authors conclude at page 2673:

> FIV and AAV5 efficiently transduce Purkinje cells and other cortical neurons with the exception of granule cells and show promise in correction of cerebellar degeneration both hereditary and acquired.

In fact, subsequent experiments proved these statements true. Using the same FIV delivery system as described in Alisky and in the present application, the authors were able to deliver and express tripeptidyl peptidase I (TPP-I), the enzyme deficient in classical late-infantile neuronal ceroid lipofuscinosis (LINCL), in Purkinje cells. This, in and of itself, provides evidence of the therapeutic benefit obtained using the claimed system.

Stein and Davidson, *Meth. Enzymol.* (2002) 346:433-454, also comment on the Alisky study above (and hence on the experiments described in the application) as follows: "Thus, an FIV vector encoding a therapeutic molecule has potential clinical value." Stein and Davidson, page 448.

Similarly, Brooks et al., *Proc. Natl. Acad. Sci. USA* (2002) 99:6216-6221, delivered both the lacZ gene and β-glucoronidase gene to adult β-glucoronidase-deficient mice using the FIV-based vectors described and used by the present inventors. As explained in the paper, the β-galactosidase gene was first delivered in order to evaluate the feasibility of the FIV system to transduce and ultimately express β-galactosidase in the CNS (see, pages 6218-6219, bridging paragraph). When the β-glucoronidase gene was delivered using the same system, therapeutic benefits were achieved. Indeed, a Commentary in the same journal touted the results using the system as "exciting" and commented that the results "are likely to have general implications for the treatment of CNS disease in LSD." Sly and Vogler, *Proc. Natl. Acad. Sci. USA* (2002) 99:5760-5762, 5760. The Commentary goes so far as to say "this study will likely be viewed as a landmark that took us well beyond the blood-brain barrier." Accordingly, Brooks and Sly

clearly evidence the usefulness of the β-galactosidase system for predicting therapeutic efficacy.

The Examiner previously disregarded Brooks, arguing that it was post-filing art and that one of skill in the art "would not have had the benefit" of the Brooks teachings. Office Action, page 6. However, the FIV system and methods used in Brooks are the same as taught in the present application and it is seminal that journal articles that post-date the applicants' filing date can indeed be provided as evidence of enablement, provided the methods used are the same or analogous. Moreover, although Brooks expressed the β-glucoronidase gene at therapeutic levels in the striatum, cerebral cortex, or hippocampus, Brooks still provides credible evidence that gene delivery methods as described in the present application can provide a therapeutic benefit and that β-galactosidase is predictive of this benefit.

Further evidence of the predictive value of β-galactosidase is shown by a number of additional references. In the interest of brevity, applicants provide three abstracts herewith directed to delivery of β-galactosidase to the CNS using various gene delivery systems. Hagihara et al., *Gene Ther.* (2000) 7:759-763, abstract, delivered the lacZ gene using an HVJ-AVE delivery system. The lacZ gene was highly expressed in a number of cells, including Purkinje cells. Based on the findings using the lacZ gene, the authors state: "We conclude that the infusion of HVJ-AVE liposomes into the cerebrospinal fluid (CSF) space is applicable for widespread gene delivery into the CNS of large animals." Similarly, Agudo et al., *Hum. Gene Ther.* (2002) 13:665-774 delivered the lacZ gene using an HSV-1 amplicon vector. Expression of the lacZ gene within Purkinje cells was persistent and was maintained for at least 40 days. The authors conclude: "These results demonstrate that HSV-1 amplicon vectors can effect safe and stable transgene expression in Purkinje cells in vivo, raising the possibility of using these vectors for long-term gene therapy of human cerebellar disorders." Additionally, Kyrkanides et al., *Brain Res. Mol. Brain Res.* (2003)

119:1-9, successfully delivered and expressed the lacZ gene in Purkinje cells using an FIV vector.

Each of the above-described studies evidences the credibility of using a β-galactosidase system to predict the therapeutic benefit in a gene therapy context. It is well settled that art recognized screening procedures and tests can be relied on to establish utility under 35 U.S.C. §112, first paragraph. As explained in *In re Brana*, 34 USPQ 1436, 1442-1443, in addressing a 35 U.S.C. §112, first paragraph rejection:

> Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

Likewise, rigorous correlation between disclosed *in vitro* utility and an *in vivo* activity is not necessary where the disclosure of pharmacological activity is reasonable based upon probative evidence. *Cross v. Iizuka*, 224 USPQ 739, 747 (Fed. Cir. 1985).

Not only have applicants provided probative evidence that the β-galactosidase system is considered predictive of therapeutic efficacy, they have also provided probative evidence that using the identical system as described in the application, a therapeutic protein, TPP-I, was expressed in Purkinje cells and provided a therapeutic benefit (see, Alisky described above). Thus, contrary to the Examiner's assertions, applicants have indeed taught how to make and use the invention and have therefore satisfied the enablement requirement of 35 U.S.C. §112, first paragraph. Accordingly, this basis for rejection has been overcome and withdrawal thereof is respectfully requested.

**Rejection Under 35 U.S.C. '112, First Paragraph**

Claims 19 and 20 stand rejected under 35 U.S.C. §112, second paragraph as indefinite because "the conclusory statement is broader in scope than the scope of the preamble." Office Action, page 7. Claims 19 and 20 have been amended in order to make the concluding statement consistent with the preamble and now recite that the method is for treating or preventing "cerebellar neuronal degeneration." Thus, this basis for rejection has been overcome and withdrawal thereof is respectfully requested.

## CONCLUSION

Applicants respectfully submit that the claims define an invention that is patentable over the art. Accordingly, a Notice of Allowance is believed in order and is respectfully requested. If the Examiner notes any further matters which she believes may be resolved by a telephone interview, she is encouraged to contact the undersigned attorney at (650) 493-3400.

Respectfully submitted,

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